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ON THE HISTOLOGY OF THE THYROID AND
PITUITARY AND ON THE BONE MARROW IN RATS

BY

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THE EFFECT OF METHYL- AND PROPYLTHIOURACIL ON THE HISTOLOGY OF THE THYROID AND PITUITARY AND ON THE BONE MARROW IN RATS

By

O. BISTRÖM

In 1941 MacKenzie et al. (14) showed in experiments on animals, a goitrogenic effect with sulphaguanidine. A similar effect was observed at about the same time on administration of different thiourea derivatives by Richter and Clisby (15) and by Kennedy et al. (10). These substances were shown to inhibit the thyroxin synthesis and as a result Astwood, in 1943, introduced them into the human thyrotoxicosis therapy. The very favourable initial results were however soon followed by reports of various complications. Agranulocytosis was one of the severest and occurred in a few instances. Later the greatest possible specific activity and the smallest possible risk of complications has been aimed at by modification of these preparations, and the derivatives now used most often are methyl- and propylthiouracil.

That the thiouracil derivatives cause typical histological changes was found already by the first investigators. MacKenzie and MacKenzie (13) found a distinct enlargement of the thyroid gland as early as after 3 to 4 days' treatment. Its blood supply increased. From a purely histological point of view, these authors found a typical hyperplasia of the follicle epithelium and rapid disappearance of the colloid. The changes increased rapidly during the first days, later their progress decreased. Astwood et al. (2) described them somewhat more in detail, and mentions principally an increase in the height of the follicle cells. They increased in number at the

same time and pushed papillomatously into the follicle lumina. The colloid disappeared fairly rapidly from the follicles. Finally they observed an increased desquamation of the hyperplastic gland cells. Hypophysectomy prevented the origination of these typical changes, as did the supply of thyroxin, but iodine had no preventive effect. It was thus clear that the pituitary furthers the effect of thiourea derivatives. The following theory has been generally accepted: The thiourea substances prevent thyroxin synthesis in the thyroid gland, and its blood level falls. The pituitary reacts by increased secretion of thyrotropin which stimulates the thyroid gland to hyperplasia. Williams et al. (19) have confirmed these observations.

The role of the pituitary gland in the effect of the thiourea derivatives on the histology of the thyroid gland makes one inclined to assume that visible changes occur in the pituitary as well. There are very few reports on this, however. Kennedy (8) and Griesbach (10) described typical changes in the anterior lobe of the pituitary, MacKenzie and MacKenzie (13) found, on administration of sulphaguanidine, a disappearance of the acidophil cells and an increase in the basophils in the anterior lobe. On the other hand, Williams et al. (19) did not find any definite changes. Naturally we do not know what effect these substances have on the human pituitary. The experimental results are thus somewhat contradictory. In this investigation I have attempted to find out the possible effect of large doses of methyl- and propylthiouracil on the bone marrow in rats. As I also saved the thyroids and the pituitaries of the experimental animals I will describe the changes observed in these glands.

METHOD

The rats used in these tests were bred at the Anatomical Institute of the University of Helsingfors. The temperature in the rooms where the rats were kept was practically constant while tests were in progress. The animals in each series were born in the same month and were almost of the same size. They were all given the diet used in the Institute. Methyl- and propylthiouracil was introduced into the powdered food as homogeneously as possible, so that a selection was hardly possible. In the first series the diet contained 0.1 per cent. methylthiouracil and the animals were somewhat older, being born in March 1946. They were killed at intervals of 7 days. The methylthiouracil content of the diet was found to

TABLE

Test animals	Sex	Weight in gr.	Treatment days	Thyroid gland		Hypophysis		
				Weight in mg.	Cell height	Acidoph. %	Basoph. %	Chromoph. %
B 1	♂	280	—	26	5.5	21.8	13.5	64.6
C 1	♂	255	—	30	6.3	35.8	10.1	54.1
D 1	♂	232	—	20	6.3	23.4	13.2	63.4
E 1	♂	242	—	27				
Methylthiouracil 0.1 % of diet								
D 3	♀	180	14	71	7.9	4.5	27.2	68.3
C 3	♀	220	21	83	8	1.8	10.1	88.1
E 3	♀	275	21	77	9.1	0.6	16.9	82.5
D 2	♀	220	28	110	9.9	0.6	9.4	90
K 1	♀	138	—	14	6.4	42.9	18.9	38.2
Methylthiouracil 0.05 % of diet								
M 1	♀	130	10	32	8.2	24.4	14.5	61.1
M 2	♀	104	20	57	11	13.5	14.1	72.4
M 3	♀	142	30	47	10.6	12.1	18.8	69.1
M 4	♀	142	40	48	10.6	2.1	18.1	79.8
M 5	♀	145	50	56	10.9	7.5	15	77.5
M 6	♀	134	60	56	10.3			
M 7	♀	150	70	65	9.6	7.6	16.8	75.6
K 2	♀	128	—	14	4.4	37.7	18.4	43.9
Propylthiouracil 0.05 % of diet								
P 1	♀	116	10	22	9.5	6.2	13.3	80.5
P 2	♀	150	20	48	9.9	2.8	10.2	87
P 3	♀	144	30	40	10.3	5.1	15.7	79.2
P 4	♀	156	40	55	10.4	0.4	8.4	91.2
P 5	♀	158	50	50	10.4	1	17	82
P 6	♀	144	56	56	10.7	0.5	15.9	83.6

be too large as none of the test animals lived longer than 28 days. The content was reduced to 0.05 per cent. and propylthiouracil was used in one of the parallel series, and methylthiouracil in the other. The animals were much younger, being born in July 1947, and all were females. Killing was quick, chloroform being used, and took place at 10 day intervals. The control animals were selected in the same way as the test animals and bred under exactly similar conditions, except for the omission of the thiourea derivatives from the diet. The rats were more tolerant to methyl- than to propylthiouracil.

Immediately after killing, bone marrow samples were taken from the femur, they were suspended in physiological saline, and smears were made on an objective glass. They were stained by the combined May-Grünwald-Giemsa method.

The pituitary and the thyroid were immediately meticulously removed and fixed according to Helly. All the thyroid preparations were stained by Delafield's eosin-haematoxylin method, by Heidenhain's azan method and by Bensley's method (3; 4). Different stainings were tried with the pituitary sections, such as Crooke-Russel, Heidenhain's azan method, etc. Kresazan and kresazan-orange staining according to Romeis proved most satisfactory and gave the most easily differentiated preparations. The cell differences and changes appeared very distinctly.

BONE MARROW

As my purpose was to induce possible morphological changes in the various bone marrow elements or changes in their relative proportions with thiourea derivatives, a fairly large dose was chosen. The first test series were thus given 0.1 per cent. methylthiouracil in the diet. The rats did not tolerate this dose at all well, as already mentioned. For that reason the dose was reduced by a half and in later series the animals were given 0.05 per cent. methyl- or propylthiouracil.

Macroscopically the bone marrow of the treated rats seemed to be distinctly more red than that of the controls, due to an increased vascularization. On microscopic examination no great differences in general were seen. The nucleated young forms did not show any marked pathological changes and the proportion between the different types of cells was not altered in any regular way. Usually the values remained within the same limits as in the controls. The divergences from these were irregular and showed no definite tendencies.

One of the rats, treated with propylthiouracil for 56 days, showed distinct pathological changes in the bone marrow, and when killed was in a very poor condition. It was completely emaciated and bled from nose and pharynx. In the bone marrow practically all the granulocytes were pathologically changed. There were many vacuoles in the cell plasma and the nucleus-plasma correlation was altered. In the bone marrow the per cent. differential count differed considerably from that in the controls. Lymphocytes occurred as 60 per cent. of all so-called white cells. Among the

different stages of the granulocytes the youngest forms were only moderately reduced, while, on the other hand, the older forms were greatly reduced.

THE THYROID

On investigation of the effect of the thiourea derivatives on the histology of the thyroid, it seemed as if rats were not very suitable as test animals, as they normally have rather active glands. The cells are of rather high types, cubical or columnar, especially in the central parts of the lobes. The follicles are irregular and contain colloid which stains blue on azan staining. Towards the periphery, in the controls, the picture showed less activity, the epithelium was low, the follicles round and regular, containing

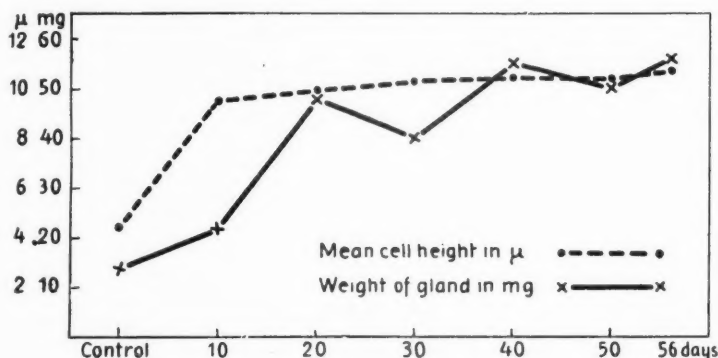


Fig. 1. — Diagram showing the mean cell height and weight of the thyroid gland in rats treated with a diet containing up to 0.05% propylthiouracil.

colloid stained red on azan staining. A distinct enlargement of the thyroid, and an increase in the vascularity was observed in the rats treated with thiouracil. When the first animals were killed after 10 days' treatment the gland was much larger and darker than in the controls. After a further 10 days these changes were strongly accentuated. The degree of change was approximately equal for methyl- and propylthiouracil (See Diagrams 1 and 2). The gland was 3 or 4 times larger after 20 days' treatment. After this the two curves still show a tendency to higher values, now they are straight with certain small irregularities due to individual differences in the rats. Such differences cannot completely be avoided

in spite of standardization. It was noticed that methyl- and propylthiouracil had similar qualitative and quantitative effects in these respects.

The thyroid gland was greatly changed microscopically. Most noticeable was the considerable increase in the height of the cells. Already after 10 days' treatment all the cells, both in the centre and periphery, are distinctly cylindrical. While the mean height in the controls was between 4.4 and 6.5 μ , it was 11 μ after 20 days'

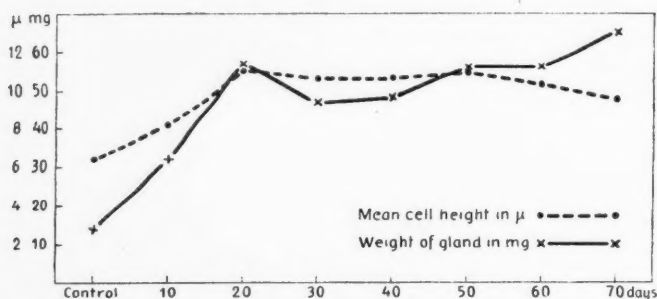


Fig. 2. — Diagram showing the mean cell height and weight of the thyroid gland in rats treated with a diet containing up to 0.05% methylthiouracil.

treatment with methylthiouracil, and 9.9 μ with propylthiouracil. Then the increase is less and the curve becomes more flat. In rats given 0.1 per cent. methylthiouracil in the diet the cell height was 9.9 μ after 21 days. Thus a higher content of methylthiouracil did not produce a greater increase in the height of the cells. This means that it was already maximal with the lower dose. The graphs show that the increase in cell height after methylthiouracil was the same as after treatment with propylthiouracil. The curves for increase of cell height correspond with the curves for the glands' total increase in weight.

Simultaneously proliferation of the cells takes place. These bulge into the lumina of the irregular follicles, both in the centre and periphery of the gland. After 10 days' treatment all the follicles are irregular.

At the same time the colloid rapidly disappears and after 10 days the follicles are almost empty. Only shrunken colloid, blue staining with azan, occurs, and then mainly in the peripheral part of the gland. Colloid, staining red with azan, of the kind that occurs in

the controls in the quiescent section of the gland, is never seen in rats treated with thiourea compounds. After prolonged treatment no colloid is contained in the follicles. The changes seem to spread from centre to periphery, as has been clearly shown above.

The vascularization is greatly increased during treatment. The capillaries are seen to be more numerous and dilatated in the section. A similar dilatation of the lymph vessels is also observed and the increase in connective tissue is marked. While the follicles of the untreated rats were separated by very thin connective tissue lamellae, the glands in the treated animals were intersected by wide strands of connective tissue, making the glands appear to be almost lobated. The small cell infiltrations in the thyroid which are observed in the control animals increase as well after the treatment. They occur, as usual, around the most active parts.

The regressive changes in the cells which occur during the treatment are characteristic of the thyroid in the animals given thiouracil derivatives. Treatment of about 10 days causes decreased staining in certain groups of cells, and just within these areas which show the greatest activity. The contours of the cells gradually become indistinct and ragged. Irregular vacuoles, staining blue with Bensley staining, arise in the cells. These gradually increase in size and in some cases fill the entire cell. After 40 to 50 days' treatment these regressive changes increase, and the majority of the cells gradually become greatly changed. A distinct fragmentation now takes place and in some parts remains of the cells are pushed in large numbers into the lumina of the follicles which often become completely filled by cell debris. That a new-formation of follicle takes place at the same time is evident. In rats treated for 50 to 60 days, small follicles with somewhat lower epithelium are seen, and a lumen which contains a little colloid which stains blue with azan staining. These seem to pass through the same development as the older follicles, and the number of new-formed follicles still seems small on that account.

In the controls, distinct apical drop-formations were observed in the more active parts of the thyroid in specimens stained by Bensley's method. These were round and distinctly demarcated. They were similar in colour to the follicle colloid but slightly paler. At the same time basal drop formations of irregular shape were observed in the high columnar cells, which may have been the same

as the basal drops described by Bensley (3; 4). As early as 10 days after treatment with methyl- or propylthiouracil, when the follicles were almost empty, no noticeable apical drop formation was observed any more, nor did it occur later during the treatment. Closer to the nucleus and at the base, irregular vacuoles, filled with blue stained colloid, were seen. They increased in size during the course of treatment, as mentioned, parallel with the regressive changes in the cells.

PITUITARY

The cells of the anterior lobe of the pituitary were classified as acidophil, basophil, and chromophobe, depending on their staining with dyes of different acidity. The cells were enumerated transversely and longitudinally through the middle of the lobe. About two thousand cells per gland were counted.

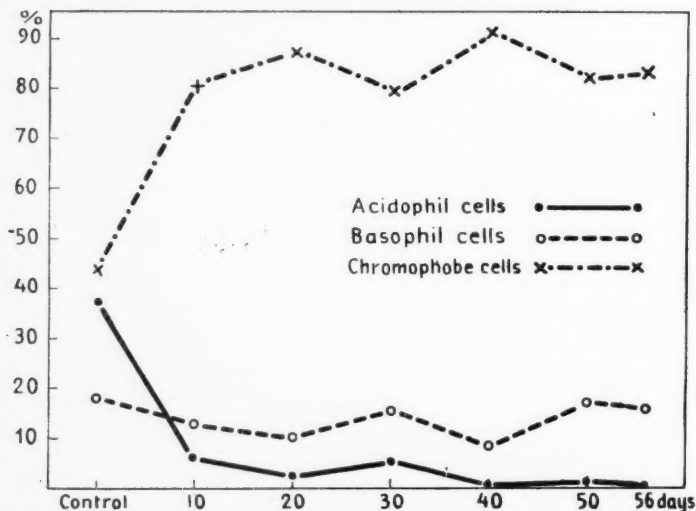


Fig. 3. — Diagram showing the distribution of hypophysis cells in rats treated with propylthiouracil.

The results are given in Table 1 and Diagrams III and IV. It is seen that methyl- as well as propylthiouracil have greatly influenced the distribution of the different kinds of cells. While the acidophil and chromophobe cells in the controls occurred in

almost equally high numbers, the chromophobe cells being about 10 per cent. more numerous, the percentage for the acidophil cells falls immediately after introduction of thiouracil derivatives. A corresponding increase in chromophobe cells corresponds to the decrease in acidophil cells. Similarly as in the changes in the thyroid gland, the greatest shift in cell elements in the pituitary occurred during the first twenty days of treatment. Later a tendency to decrease is still observed in the number of the acidophil cells and an increase in the number of the chromophobe cells. As seen from the diagrams the curves were later flat. The number of the basophil cells was almost unchanged. No definite tendency in these cells was observed in the curves.

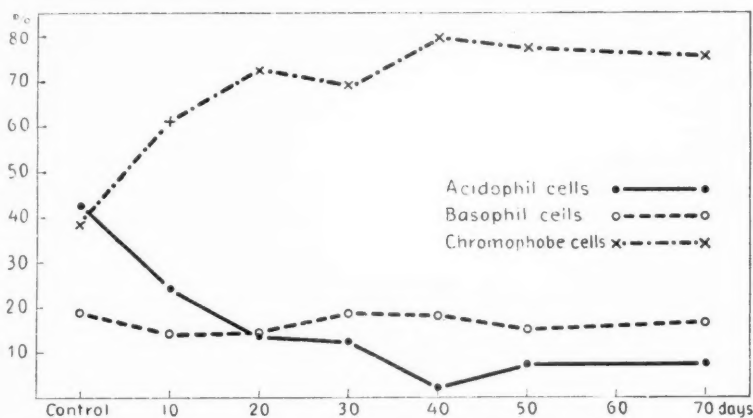


Fig. 4. — Diagram showing the distribution of hypophysis cells in rats treated with methylthiouracil.

It seems as if propylthiouracil has a stronger effect on the changes in the pituitary. The number of acidophil cells decreases still more than with the use of methylthiouracil. Complete disappearance of the acidophil cells was not observed, however. The lowest count was 0.4 per cent.

A considerable change in the shape of the acidophil cells occurred as well. In the controls the majority of cells were relatively small, with a fairly large nucleus in comparison with the cell itself. The cells were round with even edges and corresponded to Romeis' (17) young cells. During the treatment these forms disappeared. Acidophil cells with irregular shape gradually took the upper hand.

They were much greater in circumference and due to the pressure of the surrounding cells there were indentations. The nucleus in these cells was relatively small and closer in structure. The staining of plasma granulations was often hyperchromic. The young forms disappeared completely after prolonged treatment and nothing but the mature forms, already described, or the acidophil remains of cells were left.

On continued treatment a distinct increase in the number of the blue staining colloid drops was observed in the basophil cells. At the same time an increased conglomeration of extra cellular colloid, staining clear blue with kresazan staining, was observed. It was irregularly interspersed in the parenchyma of the gland.

The microscopical picture of the pituitary section was completely changed during the treatment. While the acidophil cells, staining bright red, dominated in the controls, the pituitary of the treated rats was dominated by the colloid which stained bright blue with kresazan, and the violet chromophobe cells.

DISCUSSION

Regarding the bone marrow, it seems as if the thiouracil derivatives would not, in the majority of cases, cause noticeable changes in the cell morphology in the treated rats. I observed no shifts in the percentage distribution of the different cell elements, and the cells were quite normal in type. The case described, with a course resembling agranulocytosis, was unique. The changes were typical. A decrease in the per cent. of all the granulocyte cell stages was observed, the mature forms being most decreased. This agrees with Kienle's (11) bone marrow findings in cases of human agranulocytosis caused by medicines. I observed that the cells were toxically changed, vacuolized and disturbed in their development. Everything suggests that when changes occur, they are of toxic-anaphylactic origin and arise suddenly. I do not wish to draw any parallels between rats and humans in this respect as there is no evidence. However, it should be pointed out that while typical morphological changes in the bone marrow, following administration of thiouracil, cannot in general be shown, they may evidently occur suddenly in certain individuals, their character then being analogous to that of human agranulocytosis.

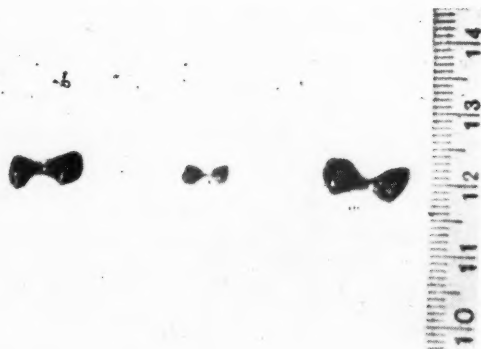


Fig. 5. — In the middle thyroid from control rat, on the left thyroid from rat fed with methylthiouracil for 50 days, and on the right thyroid from rat fed with propylthiouracil for 50 days.

Already the first investigators found that the influence of the thiouracil derivatives on the histology of the thyroid was promoted in some way by the pituitary. All recent investigations seem to show that the thyrotropin secreted from the anterior lobe of the pituitary was active here. As seen, a distinct hyperplasia of the thyroid tissue is caused by the thiouracil derivatives. The cells increase in height and become high columnar. They increase in number and bulge papillomatously into the lumina of the follicle, and the colloid disappears rapidly. The hyperplastic gland cells evidently promote its absorption into the blood. Simultaneously with this direct gland cell reaction, an increase in the connective tissue and lymph cell infiltration is observed. All these changes are also seen after injection of thyrotropic hormone. The histological picture corresponds roughly with that of human thyrotoxicosis. This fact is pointed out, but no conclusions can, however, be drawn from it.

After treatment with thiourea substances for some time no further secretion was observed in the cells. Secretion is generally considered a characteristic of the hyperplastic thyroid gland. When the first rats were killed after 10 days' treatment the follicles were empty. The output of colloid was then practically complete. In the highly active, superficial cells no appreciable secretion was observed. The vacuoles with irregular margins, contained in the cells, and whose number increased during the treatment, seemed to be an expression for the regressive changes in the cells which

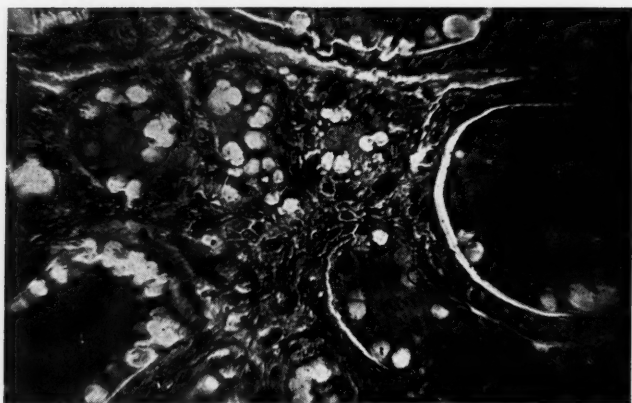


Fig. 6. — Thyroid tissue from control rat. The specimen was taken from the border between the quiescent and active part. The follicles are partly rich in colloid, the epithelium being low, partly poor in colloid, the epithelium being higher (Helly-Bensley. $\times 700$).

simultaneously became more and more pronounced. Judging from the changes observed, the gland was in a state of «emergency service».

In this state the cells evidently could not remain unchanged. As mentioned, regressive changes took place in the cells, which, after 40 to 50 days' treatment, were very conspicuous. In some parts the cell borders were irregular and the staining decreased.

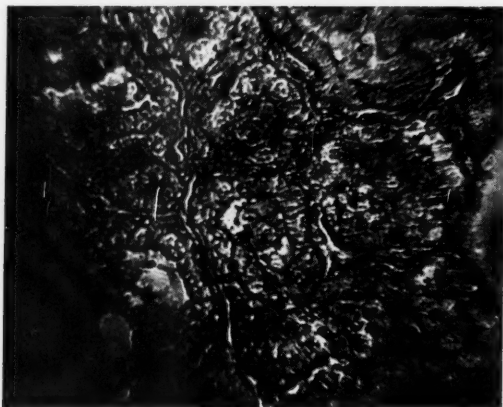


Fig. 7. — Thyroid tissue from rat fed with methylthiouracil for 60 days. The epithelial cells are high columnar. The irregular follicles contain only remains of colloid. A distinct cellular regression occurs, with diminished staining and irregular vacuoles at the base of the cells (Helly-Bensley. $\times 700$).

The vacuoles which were filled with colloid, staining blue with Bensley's staining, occurred with increased frequency. These changes increased and finally cell masses were extruded into the follicle lumina. These regressive changes are also observed in human thyrotoxicosis, although less distinctly. New follicles which rapidly pass through the same development are probably formed during the treatment.

It is thus found that on treatment with thiouracil derivatives changes occur in the thyroid gland similar to those occurring with thyrotropic hormone. It seems however as if the secretion in the cells was impeded. That the gland utilizes the colloid stored in the follicles has already been stated.

Regarding the influence of the two derivatives, methyl- and propylthiouracil, both seem to have the same effect with the doses used here, as shown by the changes in the thyroid gland. The different effects, for instance the increase in size of the gland, the increase in height of the cells, etc., were of about the same degree. The dosage was evidently too large, however, as the animals did not tolerate it well. The changes were evidently also maximal as doubling the dose did not cause greater changes. A difference in the effect of the substances might have been demonstrated with smaller doses.

It may be assumed that the thyrotrope hormone is secreted in increased quantities after treatment with thiourea derivatives and this is probably due to these substances preventing secretion of thyroid hormone. The increased secretion of thyrotropin, as it appears in the histology of the pituitary, has been studied in a large number of works. Investigations into which cell elements in the anterior lobe of the hypophysis produce the thyrotropin have been made, but no uniform results have been obtained. The majority of workers (7; 18; 12; 5) consider the basophil cells the real producers of thyrotropin, but other authors (9; 6) consider that the thyrotropin arises in the acidophil cells. Two lines have mainly been followed in the investigations. Thyroidectomy has been performed and after this the secretion of the thyroid gland naturally disappears from the blood, and in response the secretion of thyrotropin in the pituitary is increased, as in treatment with thiouracil derivatives. The pituitary in animals kept under low temperature has also been studied, as done by many other investigators. An increased

activity in the thyroid gland was observed which according to Brolin (5) is caused by an increased secretion of thyrotropin.

Thyroidectomy and thiourea derivatives produce almost similar effects: the secretion in the gland is stopped. In one case this takes place by surgical intervention, in the second by supply of a rather effective drug. This should be remembered on assessing the effects in an organ such as the pituitary which is so closely correlated to the majority of the functions of the body. The similarity of the reaction of the pituitary in these cases is however remarkable. A very great number of investigators have observed the disappearance of the acidophil cells in the anterior lobe of the pituitary after thyroidectomy. In my series of rats, treated with thiouracil derivatives the acidophil cells decreased greatly. After propylthiouracil only remains of degenerated acidophils were found while after methylthiouracil the number of these cells decreased to a few per cent. only. The effect of propylthiouracil was thus in this respect somewhat greater. Opinions differ among the various investigators regarding the reaction of the basophil cells to thyroidectomy. The majority have observed an increased vacuolization and a certain hypertrophy in these cells. The hypertrophied, vacuolized basophil cells are called thyroidectomy cells. Lebedeva (12), for instance, found no increase in their number. My results agree completely with this observation. I obtained no increase in the number of basophil cells after treatment with thiouracil derivatives, but there was an increase in the colloid vacuoles in the somewhat enlarged, often seemingly regressively changed cells. After the treatment a great increase in extra-cellular colloid was observed. Already Rogowitsch observed corresponding occurrences after thyroidectomy.

A number of investigators have subjected the pituitary of rats, kept at low temperature, to histological examination. Brolin's (5) work may be specially mentioned as it is very thorough. He found signs of a distinctly increased thyroid secretion, evidently due to increased thyrotropin secretion. The main findings in the pituitary were hypertrophy and vacuolization of the basophil cells, and their number was often increased. The acidophil cells did not show changes or shifts to any extent. Exposure to cold, which caused an increased secretion of thyrotropin, differs from thyroidectomy and treatment with thiouracil in that the secretion of the

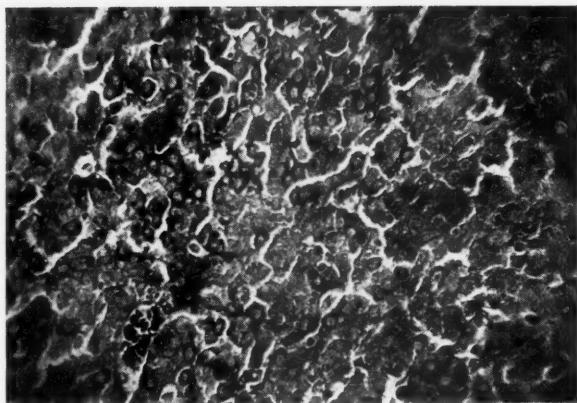


Fig. 8. — Tissue from the anterior lobe of pituitary from control rat. An abundance of acidophil cells are observed; they appear as small, round, dark cells with a fairly large nucleus (Kresazan Romeis. $\times 400$).

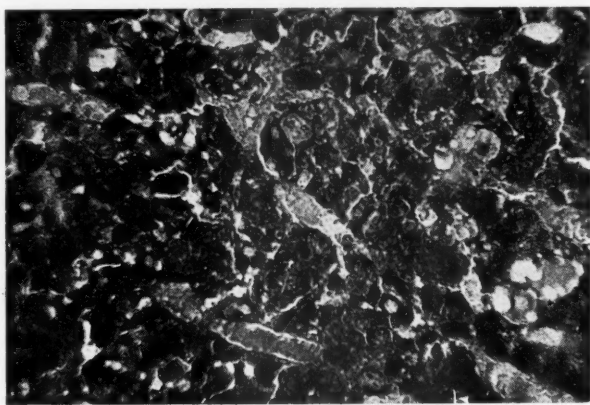


Fig. 9. — Tissue from the anterior lobe of pituitary from rat fed with propylthiouracil for 50 days. Acidophil cells do not occur. Large basophil cells are seen here and there in the photograph; in the middle there is a cell containing drops of colloid. Extracellular colloid is observed in several places (Kresazan Romeis. $\times 400$).

thyroid remains intact. In the two latter cases there is an increased thyrotropin secretion and a suspended secretion from the thyroid gland. On exposure to cold, an increased thyrotropin secretion and an increased thyroid secretion occurs. The differences in the histological findings in the pituitary must be considered due to these facts.

That the acidophil cells are the thyrotropin producing elements is less probable, owing to what has been said above. These cells disappear rapidly after thyroidectomy and administration of thiourea derivatives. In the latter case, judging from the findings in the thyroid gland, a continuous thyrotropin effect persists for weeks after the acidophil cells have disappeared almost completely from the anterior lobe of the pituitary. But, after exposure to cold, no great changes in the number of acidophil cells are observed,

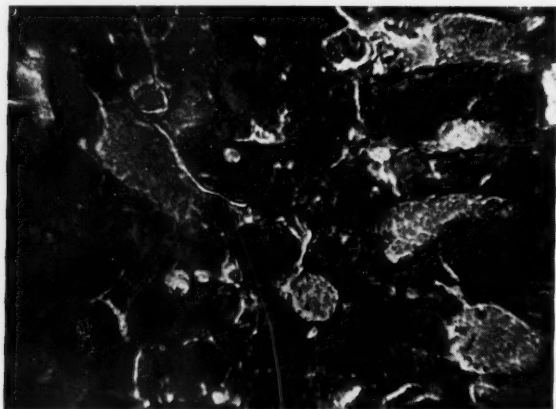


Fig. 10. — Group of large basophil cells in pituitary of rat fed with propylthiouracil for 50 days. One of the cells in the middle contains a large drop of colloid (Kresazan Romeis, $\times 1200$).

in spite of increased thyrotropin secretion. It thus seems as if the existence of the acidophil cells is dependent on an uninterrupted thyroid gland secretion. Secretion of the growth hormone is generally considered to originate in the acidophil cells. This is of great interest, considering the disturbances in growth when the activity of the thyroid gland is reduced or inhibited.

No increase in the number of basophil cells was observed after treatment with thiouracil derivatives, but there was an increased vacuolization of these cells. The results after thyroidectomy were quite similar according to Lebedeva (12). After exposure to cold Brolin (5) observed an increased vacuolization and hypertrophy of these cells, but he has not given numerical results. However, he points out the paradox that these cells show distinctly regressive changes in spite of the increased secretion of thyrotropin.

If the basophil cells were the actual producers of thyrotropin it would be rather strange if their number did not tend to increase during treatment with thiourea derivatives. The chromophobe cells which increase greatly in number can hardly be considered to secrete the thyrotropin. Jores (9) says that «symptomlessness» of the chromophobe adenomas is a point against this assumption. No signs of increased thyrotropin secretion are seen in these adenomas. It seems rather as if the increase in chromophobe cells would arise for instance in degranulation of the cells, principally the acidophil cells.

From among the classical types of cells in the anterior lobe of the pituitary the basophil cells seem the most likely to secrete thyrotropin. This has not been definitely proved however, and there are certain facts against this assumption. Their relative number does not show a marked increase and the existing cells often show distinct regressive changes. Vacuolization of other kinds of cells is also observed under these conditions. With the knowledge of the large number of hormones which are thought to originate from the anterior lobe of the pituitary and the relatively small number of types of cells which can be differentiated in this area, it seems as if a final solution of this problem could not be found with the present methods of staining.

CONCLUSION

The following facts were observed after treatment of rats with methylthiouracil or propylthiouracil:

A. *In the bone marrow:*

1. No great regular morphological changes occurred in general.
2. In one case there was a great decrease in granulocyte cells, mainly in their mature forms. The cells were toxically changed. The picture is most like that of toxic-anaphylactically caused agranulocytosis.

B. *In the thyroid gland:*

1. Hyperplasia of the epithelium with increase in height and number of cells, and a rapid disappearance of the follicle colloid occurred.

2. Simultaneously a reactive increase in connective tissue, vascularity, and lymphocytic infiltration of small cells took place.
3. The secretion decreased and disappeared almost completely when the follicle colloid disappeared.
4. Severe regressive changes in the cells gradually appeared and many of the cells were destroyed.
5. The changes, except suspension of secretion, were analogous to those described as sequelae to increased thyrotropin secretion.

C. *In the pituitary:*

1. A great decrease in the number of acidophil cells, or a complete disappearance occurred.
2. A corresponding increase in chromophobe cells,
3. an increased vacuolization of basophil cells, and
4. a great accumulation of extracellular colloid were seen.

SUMMARY

Rats were treated either with methylthiouracil or propylthiouracil. The preparation was given powdered in the food in a quantity of 0.05 per cent of the diet. The animals were killed at intervals of 10 days and the bone marrow, thyroid and pituitary glands were examined.

No morphological changes were as a rule observed in the bone marrow. Toxic changes suggestive of agranulocytosis occurred in one case only. The granulocyte cells, mainly the mature forms, were greatly decreased in number. The existing cells were vacuolized and their development disturbed.

The thyroid gland was enlarged and hyperaemic. The cells were high columnar. The follicles were empty and papillomatous. The connective tissue and the lymph cell infiltrations were increased as a reaction. The appearance of the thyroid was hyperplastic, with changes suggesting increased thyrotropin secretion. During the treatment the secretion in the cells disappeared, and later there was a marked cell regression, the cells becoming vacuolized, their edges irregular and their staining decreased. In certain parts the cells were extruded in large numbers into the lumina of the follicles.

The acidophil cells in the pituitary disappeared almost completely and did not re-appear during the treatment. The chromophobe cells increased in the same proportion. The relative number of the basophil cells remained unchanged, but an increased vacuolization, a certain hypertrophy, and signs of regression were observed in the cells. A large deposit of extracellular colloid was found.

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